UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,608	08/28/2003	Jean-Pol Cassart	B45300-1	8978

20462 7590 04/18/2007

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,608	CASSART ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 6-9 are being examined.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 remain rejected under 35 U.S.C. 112, first paragraph, as failing to provide a clear written description of ASCL2, for reasons already of record in paper of 10/27/06.

The response asserts that the amended language "ASCL2" in claim 6, which is another name for CASB7439, would obviate the rejection. The response asserts that Applicants are not claiming compositions made from new or unknown biological materials. The response asserts that rather, the currently pending claims are drawn to methods involving fragments comprising epitopes identified by Applicants of a known polypeptide, namely SEQ ID NO:2. The response recites Alders et al, asserting that at the time of filing, the genus of ASCL2 polypeptides had already been described in the scientific literature and exemplified by many homologues; much was known about its structure, including its sequence and evolutionarily conserved regions.

The response has been considered but is not found to be persuasive for the following reasons:

The claims encompass a method for inducing an immune response to a **genus of ASCL2 variants** of SEQ ID NO:2, with unknown structure and function, using any epitopte fragment of SEQ ID NO:2, in view of the disclosure in the specification that the present invention relates to CASB7349 polypeptides comprising an amino acid sequence which has at least 70%, 80%, 90%, 95% or 97-99% identity to that of SEQ ID NO:2 (p.6, lines 14-17).

Further, Alders et al only teach the human ASCL2 which is the same as SEQ ID NO:2, two corresponding proteins in mice, Mash 1 and Mash 2, and one homologue in Drosophila (p.860). The disclosed SEQ ID NO:2, two corresponding proteins in mice, Mash 1 and Mash 2, and one homologue in Drosophila are not representative species of the encompassed genus of ACSL2 variants of the claimed invention. Alders et do not teach common structure, which common structure contributes to the function of the claimed ASCL2 polypeptides.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 6-9 remain rejected under 35 U.S.C. 112, first paragraph, because the specification and the claims lack enablement for a method for inducing an immune response to ASCL2, or SEQ ID NO:2 in a human, or non-human animal, using any epitope fragment of SEQ ID NO:2, for reasons already of record in paper of 10/27/06.

1. Unpredictability of cancer immunotherapy

A. The response asserts that half of the cited references are from 1995 or earlier and do no represent the current views of the skilled artisan. The response recites Rosenberg et al, 2004, Tsuruma, 2005, and Hoos, 2007. Rosenberg teach cancer studies using MART-1, gp-100, tyrosinase, TRP-2, NY-ESO-1, MAGE-12, Her2/neu and telomerase proteins. Tsuruma teach

genes highly expressed in colorectal cancer. Hoos et al suggest a spectrum of appropriate endpoints by which to measure the efficacy of cancer vaccines. The response asserts that a review of the references cited on the preceding page will reveal that methods involving immunogenic fragments of polypeptides, like those recited in the claims, are useful as an adjuvant to other therapeutic modalities ranging from chemotherapy to surgical approaches, and that immunogenic fragments are useful in non-vaccine settings, such as adoptive immunity.

The recitation of Rosenberg et al, 2004, Tsuruma, 2005, and Hoos, 2007 is acknowledged.

The response has been considered but is not found to be persuasive for the following reasons:

Although some of the references are older than 1995, the teachings in the cited references however have not been disputed by the art, and are applicable to the instant application. Further, the teaching of Rosenberg et al collaborates the teaching of Kirkin et al, confirming the teaching of Kirkin et al that not any peptides from any cancer antigens would be useful as a vaccine for cancer therapy, and thus the unpredictability of cancer immunotherapy. Kirkin et al reviews studies of identified CTL peptides from several groups of melanonoma-associated antigens, such as MAGE, BAGE, PRAME, NY-ESO-1, tyrosinase MART-1, gp100, TRP-1, TRP-2, MUM1, CDK4, beta-catenin, gp100-in4, p15 and N-acetylglulcosaminyl-transferase V (abstract). Kirkin et al conclude that so far only a few peptides induce response to the antigens in vivo in cancer patients, and resulting in tumor regression (abstract). Similarly, Rosenberg et al teach that the scarcity of the clinical response of patients to peptide vaccination makes it difficult to validate the usefulness of sensitive in vitro technique such tetramer and ELISpot assay to detect the in

vivo generation of anti-tumor T cells (p.909, last paragraph, last four lines, and abstract). Further, as shown on table 2 in Rosenberg et al, only a few peptides of only some of numerous known cancer antigens actually are successful, such that they can be tested in cancer patient trials. Similar to Rosenberg, Tsuruma confirms the problems with immunotherapy taught by Smith et al, i.e. escape of cancer cells from the host immune system, such as downregulation of the expression of tumor antigens, or MHC molecules, loss of the ability to present the antigen to T cells, or production of suppressive cytokines (p.805, first column, last paragraph). Tsumura et al further teach that there are insufficient reports of substantial rates of tumor regression in patients with advanced cancer treated with peptide vaccine (p. 805, first column, last paragraph). In addition the teaching of Hoos et al concerning a spectrum of appropriate endpoints by which to measure the efficacy of cancer vaccines does not address the problems with unpredictability of the encompassed cancer treatment of the claimed invention, and thus is not germane here.

Concerning the response's comment that methods involving immunogenic fragments of polypeptides are useful as an **adjuvant** to other therapeutic modalities, and that immunogenic fragments are useful in non-vaccine settings, such as adoptive immunity, the response argues limitation not the claims. Further, there is no indication that the claimed peptides actually have any adjuvant effects, enhancing the effectiveness of other therapeutic modalities, such as conventional chemotherapy.

B. The response asserts that the claims do not contain requirement that the recited method successfully treats cancer. The response asserts that the claims recite a method of

inducing an immune response, and therefore White et al teaching concerning antigen internalization or down-regulation is not germane to the claimed invention.

The response has been considered but is not found to be persuasive for the following reasons:

In an immune response, the antibodies or T cells that are produced are specific and have to recognize the target antigen on cancer cells to be effective. However, due to internalization or down-regulation of the antigen or the MHC molecules, the antibodies or the T cells would not be able to recognize the target cancer cells, and thus would not be effective or useful for therapeutic application.

C. The response asserts that Kirkin et al support the conclusion that a peptide approach is viable, which is supported by Marchand et al, 1999.

The recitation of Marchand is acknowledged.

The response has been considered but is not found to be persuasive for the following reasons:

Although a peptide approach is viable, based on the teaching of Kirkin et al, and Marchand et al, the teaching of Kirkin et al clearly indicates that not any peptides of any tumor antigens are CTL peptides and/or are useful for treating cancer. It is noted that Marchand et al used the same MAGE-3 peptide taught by Kirkin et al, the only effective peptide among identifiable MAGE-1, MAGE2 and MAGE-3, MAGE-4, MAGE-6 CTL peptides as taught by Kirkin et al, for treating melanoma.

D. The response asserts that contrary to Gaiger et al, recent study by Oka et al shows that WT-1 peptide is effective and affect cancer growth in vivo.

The response has been considered but is not found to be persuasive for the following reasons:

The WT-1 peptide, amino acids 235-243 taught by Oka et al (Oka et al, p.13886, first column, second paragraph) is different from the various WT-1 peptides taught by Gaiger et al (Giager et al, p.1483, first paragraph). Reviewing the teaching of Oka et al and Gaiger et al thus confirms that not any CTL peptides of tumor antigen, even those inducing specific tumor cell lysis in vitro, and antibodies in vivo, in cancer patients, are capable of reducing cell growth of cancer cells in a patient.

E. The response again recites Hoos et al, and concludes that serious scientific questions may be raised about using tumor mass as an endpoint to evaluate WT-1 peptides.

The response has been considered but is not found to be persuasive for the following reasons:

Hoos et al teach that if early trials showing immune response, or other biologic or clinical activity, then efficacy trials, such as detecting tumor shrinkage or slowing the rate of tumor progression, may be initiated (p.1, second column, first paragraph). In other words, Hoos et al propose different steps involved in evaluation of cancer therapy, which does not address the issue of unpredictability of cancer immunotherapy.

Further, the scope of the claimed invention is reasonably interpreted as a method for treating cancer, such as reducing cancer cell growth in a human or non-human animal, via

inducing an immune response to any epitope of SEQ ID NO:2, or to the peptide SEQ ID NO:25. There is no evidence, nor one can predict that any epitope of SEQ ID NO:2, including SEQ ID NO:25 of the claimed invention could be successfully used for treating cancer, such as reducing cancer cell growth, in view of the teaching of Smith et al, White et al, Kirkin et al, Gaiger et al, Ezzell et all, Sptiler et al, all of record.

F. The response asserts that the specification discloses specific epitopes of SEQ ID NO:2, and providing guidance regarding epitopes likely to engender an immune response, and thus providing guidance to each of the points raised by Roitt et al.

The claims encompass the use of a **genus** of epitopes of SEQ ID NO:2 for inducing an immune response in a human or non-human animal. Although the specification discloses three overlapping peptides, peptides 23-25, and another peptide, peptide 16, that induce in vitro T cell response to full length SEQ ID NO:2 (Example 10 on pages 68-71), one cannot extrapolate from these few CTL peptide to the encompassed genus of epitopes of SEQ ID NO:2 that can induce CTL response, especially in vivo in a cancer patient, because different T cell epitopes have different structure and properties, and because only a minority of peptide fragments of a proteins are CTL epitopes in view of the teaching of Roitt et al, of record. This is also shown in the specification, in which peptide 21, although induces CTLs recognizing the peptide, said CTLs do not recognize full length SEQ ID NO:2 (p. 69). Further, although the specification discloses two peptides, one of which induces antibody specific for SEQ ID NO:2 on colon cancer cells (p.72, Example 11 on page 71), and although any peptides of a protein can be used to make antibodies, however, whether the antibodies recognize the full length SEQ ID NO:2 in three dimensional structure, as on cell surface in a human or non-human animal, is not predictable, because not any

epitope is exposed on the surface of the protein and of the cells, in view of the teaching of Roitt et al, of record.

Further, screening assays do not enable the claimed invention because the court found in *Rochester v. Searle*, 358 F.3d 916, Fed Cir, 2004, that screening assays, and by inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

2. The claims encompass a method for treating cancer, as contemplated in the specification, via inducing an immune response.

The response asserts that it is improper to interpret that the claims encompass a method for treating cancer. The response asserts that none of the claims recite treating cancer, nor successful treatment limitation.

The response has been considered but is not found to be persuasive for the following reasons:

The claims are reasonably interpreted as a method for treating cancer, such as reducing cancer cell growth in vivo, via induction of an immunoresponse, using any peptide epitope of SEQ ID NO:2, or the peptide SEQ ID NO:25.

The response asserts that the rejection ignores that a fusion partner or an adjuvant could be used with the claimed peptide. The response asserts that in Example 10, several peptides which overlap the epitope of SEQ ID NO:25 are specifically recognized by CD4+ T cells.

The response has been considered but is not found to be persuasive for the following reasons:

There is no indication that the addition of fusion partner or an adjuvant would render any peptide fragments of SEQ ID NO:2 a CTL epitope, or inducing antibodies that would recognize SEQ ID NO:2 on a cell surface in a human or a non-human animal, in view that not any peptide fragments of a protein are CTL epitopes, or could induce antibodies that would recognize the protein in its three-dimensional structure as on cell surface in vivo, in view of the teaching of Roitt et al, of record.

Moreover, although three disclosed peptides, peptides 23-25, which overlap the epitope of SEQ ID NO:25 are specifically recognized by CD4+ T cells, one cannot predict that SEQ ID NO:25 would be recognized by CD4+ T cells, and/or bind to CD4+ T cells with sufficient affinity, because SEQ ID NO:25 only has 9 amino acids in length, and because CD4+ T cells bind class II molecules, which accommodate longer peptides, i.e. more than 12 amino acids Roitt et al, 1998. Immunology, 4th ed, Mosby, London, p. 5.6.

The response asserts that Jubb et al show that both human and murine variants of ASCL2 are upregulated in cancer. The response asserts that Schmid and Conner discuss gene products other than ASCL2.

The recitation of Jubb et al is acknowledged.

The response has been considered but is not found to be persuasive for the following reasons:

The encompassed genus of ASCL2 variant are not limited to the mouse variants. For example, the ASCL2 variants could be any products produced by spliced variants of the nucleic acid encoding SEQ ID NO:2. The expression levels of the encompassed ASCL2 variants of the claimed invention are not disclosed, nor can be predicted, in view of the teaching of Schmid et al and Conner et al.

The response asserts that a requirement of a successful cancer treatment to the same degree that might be found in clinical trials would be inappropriate.

The response has been considered but is not found to be persuasive for the following reasons:

A successful cancer treatment, such as reducing cancer cell growth in a human, does not require the same degree as that of clinical trials.

For the reasons set forth above and in previous Office action, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
April 05, 2007

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600